

Effects of exercise interventions on cardiovascular health in individuals with chronic, motor complete spinal cord injury

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BMJ Open Effects of exercise interventions on cardiovascular health in individuals with chronic, motor complete spinal cord injury: protocol for a randomised controlled trial [Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (CHOICES) Study]

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ABSTRACT

Introduction Recent studies demonstrate that cardiovascular diseases and associated complications are the leading cause of morbidity and mortality in individuals with spinal cord injury (SCI). Abnormal arterial stiffness, defined by a carotid-to-femoral pulse wave velocity (cfPWV) ≥ 10 m/s, is a recognised risk factor for heart disease in individuals with SCI. There is a paucity of studies assessing the efficacy of conventional training modalities on arterial stiffness and other cardiovascular outcomes in this population. Therefore, this study aims to compare the efficacy of arm cycle ergometry training (ACET) and body weight-supported treadmill training (BWSTT) on reducing arterial stiffness in individuals with chronic motor complete, high-level (above the sixth thoracic segment) SCI.

Methods and analysis This is a multicentre, randomised, controlled, clinical trial. Eligible participants will be randomly assigned (1:1) into either ACET or BWSTT groups. Sixty participants with chronic (>1 year) SCI will be recruited from three sites in Canada (Vancouver, Toronto and Hamilton). Participants in each group will exercise three times per week up to 30 min and 60 min for ACET and BWSTT, respectively, over the period of 6 months. The primary outcome measure will be change in arterial stiffness (cfPWV) from baseline. Secondary outcome measures will include comprehensive assessments of: (1) cardiovascular parameters, (2) autonomic function, (3) body composition, (4) blood haematological and metabolic profiles, (5) cardiorespiratory fitness and (6) quality of life (QOL) and physical activity outcomes. Outcome measures will be assessed at baseline, 3 months, 6 months and 12 months (only QOL and physical activity outcomes). Statistical analyses will apply linear-mixed modelling to

Strengths and limitations of this study

- Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (CHOICES) is the first trial to compare the effectiveness of two conventional exercise modalities: (1) active upper-body arm cycle ergometry training and (2) passive lower extremity body weight-supported treadmill training across a plethora of health outcomes.
- Unlike other interventions in this population, participants are somewhat homogeneous (ie, cervical and high thoracic motor complete spinal cord injury (SCI)).
- The diversity of cardiovascular outcomes collected in the CHOICES trial is unique, including assessments of both novel and traditional cardiovascular risk factors.
- The techniques employed to measure various outcomes in this study have been shown to be valid and reliable, specifically in individuals with SCI.
- Limitations of this trial are: the lack of a follow-up time point for physiological outcomes to ascertain whether favourable adaptations persist beyond the intervention period and lack of blinding (masking) of outcome assessors to intervention allocation.

determine the training (time), group (ACET vs BWSTT) and interaction (time \times group) effects on all outcomes.

Ethics and dissemination Ethical approval was obtained from all three participating sites. Primary and secondary outcome data will be submitted for publication in peer-reviewed journals and widely disseminated.

Trial registration number NCT01718977; Pre-results.

Trial status Recruitment for this study began on January 2013 and the first participant was randomized on April 2013. Recruitment stopped on October 2018.

BACKGROUND

Inactivity related chronic diseases, such as cardiovascular disease (CVD) and type 2 diabetes mellitus, occur at a heightened frequency and earlier in the lifespan in individuals with spinal cord injury (SCI) compared with able-bodied individuals.^{1 2} Individuals with high-level, motor complete SCI appear to be at greatest risk of developing cardiometabolic disease.^{3 4} The reasons for this are multifactorial. Not only are these individuals more sedentary⁵ but injuries sustained at or above the sixth thoracic level ($\geq T6$) can disrupt autonomic pathways (ie, neural control over cardiac muscle, smooth muscle and glands),^{6 7} which consequently perturbs cardiovascular homeostasis. Such injuries can therefore impair cardiovascular responses to exercise,⁸ alter circadian oscillations in blood pressure (BP)^{9 10} and produce autonomic dysreflexia (AD),¹¹ which is an acute episodic bout of hypertension. It has been suggested that such instabilities in BP could contribute to vascular injury and consequently result in a greater risk for arterial disease in individuals with SCI.¹²

Beyond the pathological concerns of BP lability, immobilisation postinjury can lead to rapid changes in arterial structure and function as the cardiovascular system adapts to revised metabolic demands. Remodelling of peripheral arteries in the paralysed lower extremities (ie, reductions in diameter and flow in the femoral artery) occur within as little as 6 weeks postinjury.¹³ While systemic remodelling of the resistance arteries likely takes longer, aortic pulse wave velocity (aPWV), which is a measure of central artery stiffness, has been shown to be significantly elevated in men with SCI compared with age-matched, sex-matched, height-matched and weight-matched controls.¹⁴ This is of clinical relevance given aPWV has been directly linked with cardiovascular mortality, fatal and nonfatal coronary events and fatal stroke in able-bodied individuals.^{15 16} Moreover, aPWV has been shown to have cardiovascular prognostic value above and beyond that of traditional risk factors, such as age, sex, BP, cholesterol, diabetes and smoking.^{17 18} Pulse wave velocity is largely determined by the elastic properties of the artery¹⁹ and is measured as the velocity of the arterial BP wave as it travels a known distance between two anatomical sites, commonly the carotid and femoral arteries. Although aPWV is still commonly used in the literature, a more accurate terminology is carotid-to-femoral pulse wave velocity (cfPWV), which shall be used from here forward. Sympathetic tone changes in individuals with high-level SCI are important to consider when measuring the peripheral vasculature. However, the measure of cfPWV is specifically a measure of central conduit artery stiffness, not peripheral muscular artery stiffness. Therefore, we contend that conduit artery

stiffness is more likely a result of structural changes in collagen and elastin deposition in the artery itself (thus representative of atherosclerotic vascular disease), rather than changes in the sympathetic tone of the artery per se.

Exercise interventions to improve cardiovascular health in individuals with chronic SCI

Given the prevalence of inactivity in individuals with SCI⁵ and the well-accepted evidence in able-bodied individuals that physical activity confers multiple beneficial effects,^{20–22} it is logical to hypothesise that increasing physical activity through exercise may reduce CVD risk in individuals with SCI. However, a recent 16-week randomised controlled trial, whereby participants performed ≥ 40 min/week moderate-to-vigorous upper body exercise and resistance training, showed no improvement in CVD risk factors (ie, arterial stiffness, endothelial function, body composition parameters and metabolic profile).²³ Moreover, cross-sectional data suggest that objectively measured physical activity is not associated with biomarkers of cardiometabolic disease risk in individuals with paraplegia.²⁴ Given these findings, the small sample sizes and considerable variability in the existing exercise training literature in individuals with SCI with regards to (1) the exercise intervention tested (ie, exercise modality, frequency, duration, intensity), (2) participant demographics, (3) research design and (4) outcome measures collected, it is currently challenging to provide evidence-based exercise prescriptions.

Two popular training modalities employed in the SCI community are arm cycle ergometry training (ACET) and body weight-supported treadmill training (BWSTT). Given the loss of motor function in the lower limbs, upper extremity exercise via ACET is a common and practical choice for increasing physical activity in individuals with SCI in community settings. While improvements in cardiorespiratory fitness, power output and certain cardiometabolic risk factors (ie, insulin sensitivity and inflammatory cytokines) have been observed with moderate-intensity ACET in individuals with SCI,^{25–27} little is known regarding its impact on arterial stiffness and endothelial function. In terms of upper body aerobic exercise, it is notable that blood flow to the lower limbs does not change during arm crank exercise in individuals with SCI,²⁸ which may limit ACET-induced improvements in autonomic function and vascular adaptations at the systemic level. Thus, ACET may not provide the necessary physical (BP and flow) and metabolic stresses to alter vascular function below the level of the lesion among individuals with motor complete SCI.

BWSTT has predominantly been used as a rehabilitation intervention to stimulate plasticity within the spinal cord²⁹ and to promote the recovery of walking in individuals with motor incomplete SCI.^{30 31} Nevertheless, emerging data indicate that BWSTT also improves blood lipid profile, glucose tolerance, insulin sensitivity, body composition and autonomic regulation of cardiovascular function.^{32–34} In experimental rodent models of

SCI, passive hind-limb cycling also improves cardiac function³⁵ and reduces the severity of AD.³⁶ Although walking is passive, locomotion is usually initiated by robotic assistance, manually by physical therapists, or transcutaneous electrical stimulation,³⁷ the cyclical movements of the large muscles in the legs combined with the upright posture provide a considerable challenge to the cardiovascular system, potentially promoting positive training adaptations. For these reasons, it is believed BWSTT may provide a more superior exercise modality for individuals with motor complete SCI.

Trial objectives

To determine whether BWSTT has beneficial effects, over and above ACET, on arterial stiffness (measured via cFPWV) and secondary health outcomes: (1) cardiovascular parameters, (2) autonomic function, (3) body composition, (4) blood haematological and metabolic profile, (5) cardiorespiratory fitness and (6) quality of life and physical activity outcomes in individuals with chronic (≥ 1 year postinjury), motor complete, cervical and high-thoracic SCI. In comparison with ACET, we hypothesise that, through large muscle mass involvement and postural challenge, the physical and metabolic stimuli of BWSTT will reduce cFPWV by 1 m/s in individuals with established risk (ie, cFPWV \geq norm median value of age-matched able-bodied individuals at baseline).³⁸ Changes >1 m/s likely represent true changes in health status in individuals with SCI.³⁹

METHODS AND ANALYSIS

Study design and setting

The Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (CHOICES) study is a prospective, multicentre, randomised controlled clinical trial. An overview of the planned experimental design is illustrated in [figure 1](#). The trial will involve an initial or baseline assessment period, followed by assessments at 3 months and 6 months of exercise training and a 6-month follow-up assessment (12 months), for quality of life and physical activity outcomes. All testing and exercise training will take place at three Canadian sites: (1) International Collaboration On Repair Discoveries (ICORD) at the University of British Columbia in Vancouver, (2) McMaster University in Hamilton, and (3) the Lyndhurst Centre, Toronto Rehabilitation Institute – University Health Network in Toronto.

Recruitment

Participants ($n=60$) will be recruited from the three aforementioned study sites ($n\sim 20$ at each site). Potential participants will be identified through a variety of recruitment strategies including: (1) posters, which will be distributed among hospital locations and local community venues (excluding local sports venues and community programme centres), (2) social media advertising (ie, websites, Facebook and Twitter), (3) a letter

of introduction outlining the purpose of the study and (4) at the individual's request. Inclusion and exclusion criteria are outlined in [table 1](#).

Randomisation

Eligible individuals will be randomly assigned (1:1) to either treatment ACET or BWSTT. Groups will be stratified by injury level (cervical and thoracic) and age (≤ 30 years and >30 years). Allocation will be concealed using a central, web-based computer randomisation service (Empower: <http://www.empowerhealthresearch.ca/>). A statistician independent of the trial will generate the randomisation sequence; permuted blocks of varying size will be employed.

Patient and public involvement (PPI)

Patients and community-dwelling individuals with SCI were not formally involved in the development of the trial (ie, formulating the research questions, design of the study or the selection of outcome measures) from a classical PPI perspective. However, we would like to emphasise that the majority of individuals with SCI consider exercise important for functional recovery.⁴⁰ Informal conversations and feedback from individuals with SCI was taken into consideration. A number of the study team were and still are actively engaged with the wider SCI community and pertinent information was incorporated into this study protocol.

Exercise interventions

The exercise interventions will be implemented three times per week, with the aim for participants to complete continuous exercise, 30 min per session for ACET and 60 min per session for BWSTT, over a period of approximately 24 weeks ($n=72$ exercise sessions). During the trial, participants will be asked not to alter their physical activity, diet or medications. Should a change in lifestyle behaviours occur, participants will be encouraged to report to the study coordinators to document these changes and assess their impact on trial eligibility. Participants are expected to attend at least 75% of the planned exercise training sessions ($n>54$). Adherence will be periodically assessed at 8 weeks and 16 weeks to determine feasibility of intervention completion for each participant. Given the real-world nature of this trial, and the associated complexities of working with this population (ie, frequent medical appointments or complications and transportation issues), there will be an opportunity for participants to compensate for missed exercise sessions as described in [figure 2](#). Participants unable to comply with the adherence criterion will be asked to withdraw from the trial. Prior to randomisation, all participants will be asked to perform a familiarisation training session to establish their baseline exercise capacity [ie, tolerable weight support/speed, height of the ergometer, rate of perceiving exertion (RPE) and heart rate (HR)].

RPE will be recorded between bouts and at the end of each training session using the Borg scale. For safety

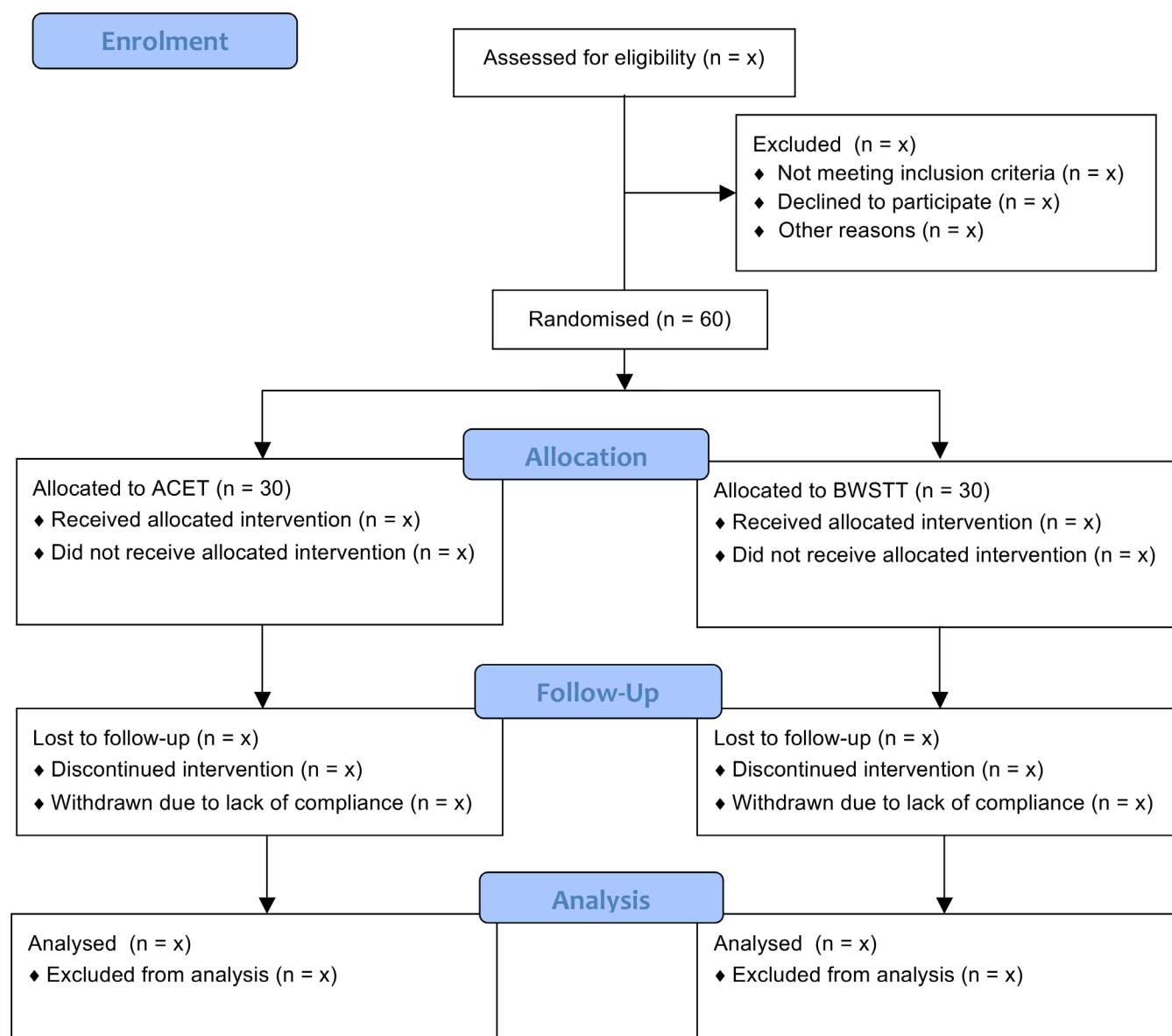


Figure 1 Trial flow chart. ACET, arm cycle ergometry training; BWSTT, body weight-supported treadmill training.

reasons, stop criteria for individual exercise sessions for each intervention will be set at a rating of 14 on the 6–20 Borg scale,⁴¹ a systolic BP change ± 30 mm Hg from resting condition, a HR < 50 bpm or > 150 or symptoms of AD (ie, pounding headache, heart palpitations and upper body flushing/sweating) or orthostatic hypotension (OH) (ie, light-headedness, dizziness and changes in vision). With these conditions, participants will rest for 5 min and will be asked if they want to stop or resume the exercise session.

Example exercise intensity progressions for both exercise interventions are outlined in table 2. These progressions are only suggestions for resistance (ACET) and speed (BWSTT). ACET prescribed at 3×30 min per week is in accordance with the updated SCI-specific exercise guidelines to achieve cardiometabolic health

benefits⁴² and should reduce the risk of an overuse injury. Currently, no guidelines exist for the most appropriate volume of BWSTT in persons with motor complete SCI; the 60 min duration was chosen based on prior BWSTT interventions.^{33 43} Furthermore, due to the passive nature of BWSTT, we anticipated that participants in this intervention arm will experience lower exercise session RPEs. Therefore, BWSTT exercise sessions will be longer in duration to approximate the training load between the two groups.

Arm cycle ergometry training

ACET will be performed on a wall-mounted arm cycle ergometer (Lode BV, Groningen, The Netherlands; Vancouver site, Monark 881E, Monark Exercise AB, Vansbro, Sweden; Toronto and Hamilton sites) against

Table 1 Participant inclusion and exclusion criteria**Inclusion criteria**

1. Adults 18–60 years of age.
2. Sustained a motor complete (AIS, A or B) traumatic SCI between the fourth cervical (C4) and sixth thoracic (T6) level ≥ 1 year prior.
3. Competent to provide informed consent.
4. Able to commit to three 60 min exercise sessions per week for 24 weeks.
5. A cfPWV \geq norm median value of age-matched able-bodied individuals³⁸
 - a. < 30 years=6.1 m/s.
 - b. 30–39 years=6.4 m/s.
 - c. 40–49 years=6.9 m/s.
 - d. 50–59 years=8.1 m/s.
 - e. ≥ 60 years=9.7 m/s.

Exclusion criteria

1. History and/or symptoms of CVD or cardiopulmonary problems/disease.
2. Major trauma or surgery within the last 6 months.
3. Active stage 3 or 4 pressure ulcer (based on the National Pressure Ulcer Advisory Panel classification).
4. Recent (within 1 year) history of lower extremity fracture or non-union fracture.
5. Any unstable medical/psychiatric condition or substance abuse disorder that is likely to affect their ability to complete this study.
6. Individuals with active medical issues such as urinary tract infections, hypertension or heart disorders.
7. Any cognitive dysfunction or language barrier that would preclude participants from following English instructions.
8. Weighing >135 kg (absolute weight capacity of the body weight-supported treadmill).
9. Participants may be excluded at the discretion of the principal investigator due to unforeseen behavioural or safety issues.

AIS, American Spinal Injury Association Impairment scale; cfPWV, carotid-femoral pulse wave velocity; CVD, cardiovascular disease; SCI, spinal cord injury.

individually determined levels of resistance [figure 3A](#). This protocol can be successfully implemented in individuals with upper cervical SCI by using tensor bandages to secure the participants' hands to the ergometer.⁴⁴ The height of the ergometer will also be electronically positioned so that the crank apex will be at or lower than the height of the participants' shoulders. Participants will be asked to keep the cadence >50 revolutions per minute (rpm). During the initial stages of training, participants will have 5 min rest periods between bouts as outlined in [table 2](#).

Body weight-supported treadmill training protocol

The protocol for BWSTT used in this trial is based on the experience of the investigative team and prior publications.^{43 45} The locomotor training protocol will consist of training individuals on a treadmill (Woodway, Weil am Rhein, Germany; Vancouver and Hamilton sites, Thera-Stride, Innoventor St Louis, Missouri, USA; Toronto site) using a body weight-support system (Andago, Hocoma AG, Volketswil, Switzerland). A minimum of two trainers will perform BWSTT [figure 3B](#). At the Vancouver site, students from the Kinesiology School at the University of British Columbia will assist with the training after receiving appropriate guidance from physiotherapists with BWSTT experience. Skin checks will be performed prior to and after each training session to ensure the participant is not experiencing shear or developing tissue injury from the harness. Where appropriate, adjustments to the harness will be provided. During the initial stages of training, participants will be allowed to have 5 min rest periods between BWSTT bouts as described in [table 2](#), where they will be lowered into a seated position to avoid syncope between walking intervals.

Assessments

Following screening and the provision of informed consent, participants will be enrolled into the trial. The collection of primary (baseline, 3 months and 6 months) and secondary (baseline, 6 months and 12 months) outcome measures ([table 3](#)) will be performed by an assessor who is unblinded to the participants' group allocation. This trial is consistent with the Standard Protocol Items: Recommendations for Interventional Trials guidelines.⁴⁶ To ensure fidelity of assessments, the principal investigators (PIs) and personnel from all sites had an initial face-to-face meeting where standardised training was performed. Common standardised operating procedures will be adhered to across all sites and regular 6-month video conferences will be arranged to serve as refreshers for study personnel. Moreover, the executive committee (consisting of trial PIs and research coordinators) will convene regularly to discuss any data collection issues that might arise.

Primary outcome measure: arterial stiffness

Following a 4-hour fast, cfPWV will be measured in the supine position following 10 min of rest. Arterial pressure waveforms will be collected at the carotid and femoral arterial sites for a minimum of 30 s using applanation tonometry⁴⁷ (model SPT-301; Millar Instruments, Houston, Texas, USA). Waveforms will be band-pass filtered (2–30 Hz) and the arrival of waveforms at each site will be identified as the minimum value of the filtered signal. cfPWV will be calculated by dividing 80% of the distance between measurement sites by the pulse transit time collected over 10 s. Pulse transit time will be determined as the time delay between the arrival of

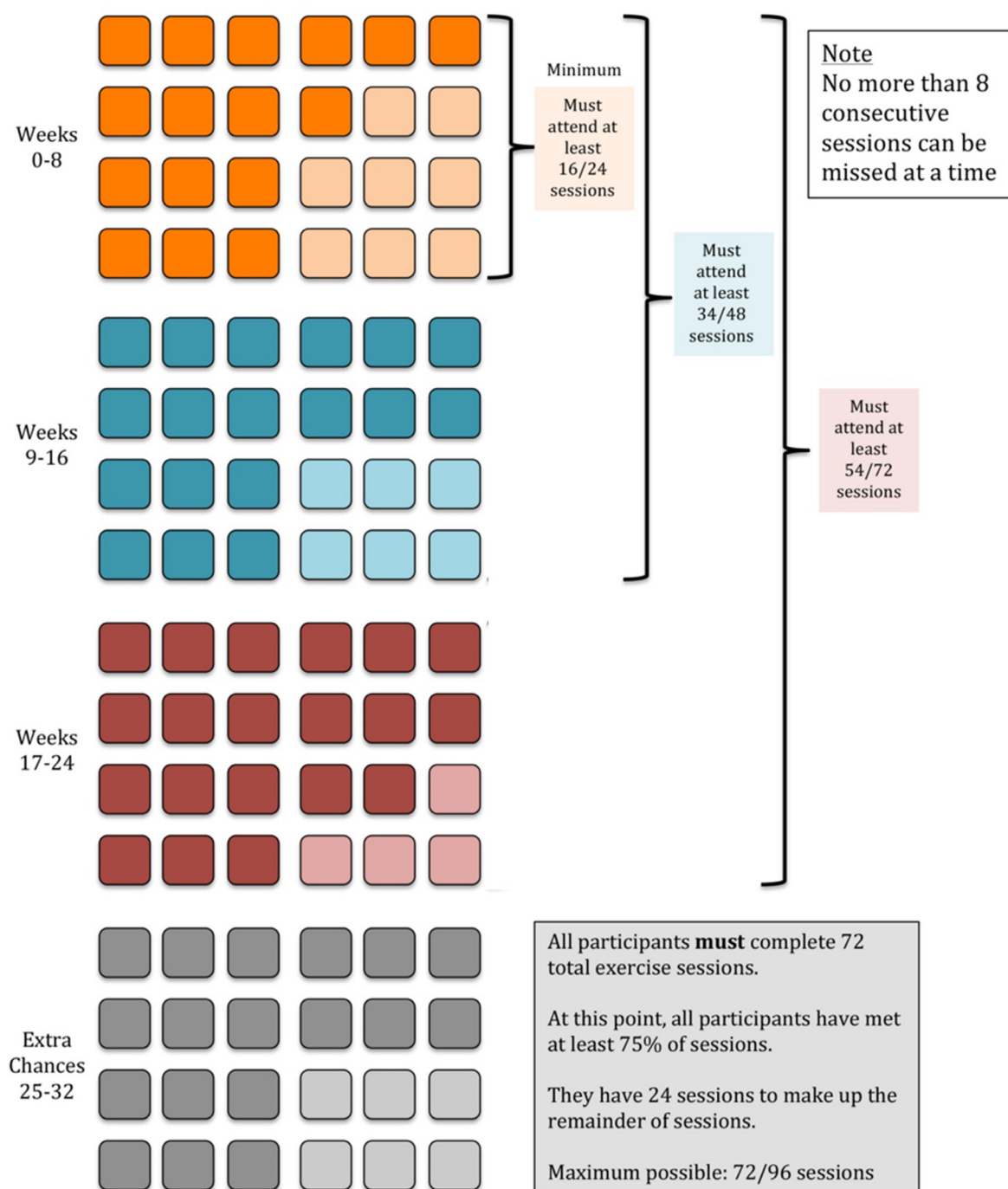


Figure 2 Adherence infographic.

the waveform at the carotid and femoral sites. Distance between the sites will be measured along the surface of the body using anthropometric measuring tape held parallel to the testing table. The mean of two 10s collections will be analysed, and if their difference is >0.5 m/s, a third 10s section will be analysed and the median of the three values will be reported. HR will be determined from concurrent single-lead electrocardiography (model ML 123, ADInstruments, Colorado Springs, Colorado, USA), while BP will be measured in triplicate (the mean will be used for analysis) from the left arm following data

collection (Dinamap Carescape V100; GE Healthcare, Buckinghamshire, UK). We have previously demonstrated acceptable inter-rater and intra-rater reliability of this assessment for persons with SCI in our laboratory.⁴⁷

Secondary outcome measures

Cardiovascular parameters

Left ventricular structure and function (Vancouver site only)

Parasternal and apical views of the left ventricle will be collected using two-dimensional echocardiography (Vivid 7, GE Healthcare, Horton, Norway) and analysed offline

Table 2 Example progression of arm cycle ergometry training (ACET) and body weight-supported treadmill training (BWSTT)

ACET					
Week	Resistance (W)	Cycling rate (rpm)	Bout duration (min)	Bouts	Total duration (min)
1	0	50	5	3	15
2	5	50	5	4	20
3	10	50	5	5	25
4	10	50	5	6	30
5	10	50	10	3	30
6	15	50	15	2	30
7	15	50	30	1	30
8	15	50	30	1	30

BWSTT					
Week	Body-weight support (%)	Speed (km/hour)	Bout duration (min)	Bouts	Total duration (min)
1	100	1.00	10	3	30
2	100	1.00	15	2	30
3	100	1.00	15	3	45
4	100	1.00	30	1	30
5	100	1.00	30	2	60
6	100	1.25	30	2	60
7	100	1.25	60	1	60
8	100	1.25	60	1	60

using a dedicated software system (EchoPAC; GE Healthcare, Horton, Norway) according to the recommendations of the American Society for Echocardiography.^{48–50}

All indices will be determined from the average of three cardiac cycles and will include measures of left ventricle structure, global systolic and diastolic function, and mechanics. The research team have considerable

expertise with assessing these indices in persons with SCI.^{51 52} Echocardiography will only be performed at the Vancouver site.

Orthostatic intolerance: sit-up test

The presence or absence of OH will be determined using a sit-up test, which we have previously shown to be a reliable assessment in individuals with SCI.⁵³ Prior to testing, participants will be instructed to empty their bladder to minimise the risk of reflex sympathetic activation. Participants will be secured to a specialised table (Sonesta Linak; Solna; Sweden) (except at the Hamilton site where investigators will passively sit participants up) and passively moved to an upright position for 15 min, following 10 min of supine rest. Participants will be instructed not to assist with the manoeuvre and the test will be terminated early should they experience severe symptoms of presyncope. HR and BP will be measured continuously via single-lead ECG (Model ML132; ADInstruments, Colorado Springs, Colorado, USA) and by a non-invasive BP machine that places a cuff on the right middle finger (Finometer PRO; Finapres Medical Systems, Amsterdam, The Netherlands), respectively. BP will also be measured at 1 min intervals using an automated device (Dinamap Carescape V100; GE Healthcare, Buckinghamshire, UK) with a cuff placed on the left upper arm. OH will be defined as a decline in systolic BP ≥ 20 mm Hg or diastolic BP ≥ 10 mm Hg when upright.⁵⁴

BP lability: 24-hour BP monitoring

The monitoring of 24 hour BP is based on the previous experience of the study team.⁵⁵ Continuous BP monitoring

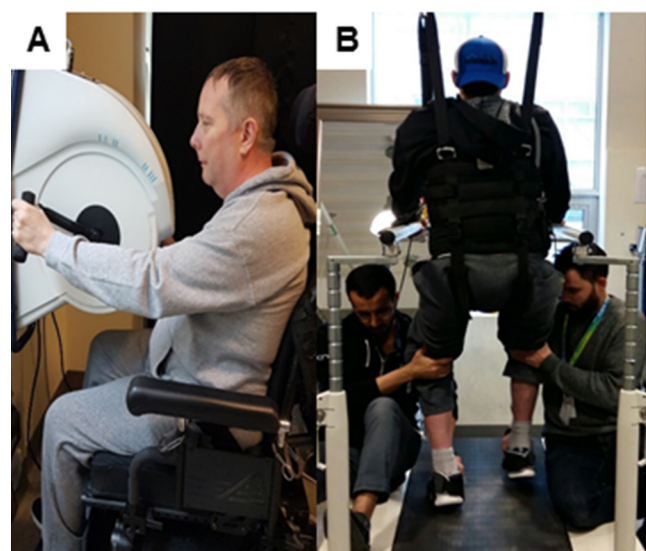



Figure 3 Participants actively performing arm cycle ergometry training (ACET) (A) and passive (assisted) body weight-supported treadmill training (BWSTT) (B). The participant and staff members (AAA and TEN) in panels A and panel B, respectively, provided consent to publish these images.

Table 3 Summary of assessments at each time period

Study period					
	Enrolment	Allocation	Post allocation (T_{months})		
Time point	T_{baseline}	0	T_3	T_6	T_{12}
Enrolment					
Eligibility screen	X				
Informed consent	X				
Familiarisation sessions	X				
Allocation					
		X			
Interventions:					
• ACET • BWSTT					
Assessments:					
primary outcome:					
Arterial stiffness	X		X	X	
Secondary outcomes:					
1. Cardiovascular parameters					
1.1 Left ventricular function structure*		X	X	X	
1.2 Orthostatic instability		X		X	
1.3 Blood pressure lability*		X		X	
2. Autonomic function					
2.1 Sympathetic skin response†		X			
2.2 International autonomic standards evaluation†		X		X	
3. Blood sample					
3.1 Haematological profile and cardiovascular disease risk biomarkers		X		X	
4. Body composition					
4.1 Fat free mass and fat mass		X		X	
4.2 Waist and hip circumference		X		X	
4.3 Body mass index		X		X	
5. Cardiorespiratory fitness					
5.1 Peak oxygen uptake		X		X	
5.2 Pain scale		X		X	
5.3 PANAS		X		X	
6. Quality of life					
6.1 MOS SF-36 pain and general health		X	X	X	X
6.2 Satisfaction with life scale		X	X	X	X
6.3 Life satisfaction questionnaire		X	X	X	X
6.4 Self-care, mobility, respiratory and sphincter management		X	X	X	X
6.5 Self-efficacy for aerobic exercise		X	X	X	X
6.6 Impact on participation and autonomy questionnaire		X	X	X	X
6.7 Leisure time physical activity		X	X	X	X

*Data only collected at the Vancouver site.

†Data only collected at the Vancouver and Hamilton sites.

ACET, arm cycle ergometry training; BWSTT, body weight-supported treadmill training; MOS SF-36, medical outcome survey short form-36; PANAS, positive and negative affect scale

will be recorded over 24 hours outside the laboratory (Meditech ABPM-04, Budapest, Hungary) for participants at the Vancouver site only. BP will be measured at 30 min

intervals between 06:00 and 09:00, at 15 min intervals between 09:00 and 21:00, and every hour between 21:00 and 06:00. Severity of AD, OH and subjective symptoms

(eg, light-headedness and dizziness) will also be assessed using a validated autonomic questionnaire.

Autonomic function

Sympathetic skin responses (SSRs)

The qualitative interpenetration of SSRs has been shown to be a reliable measure for assessing sudomotor function in persons with SCI⁵⁶ and will be assessed at baseline for participants at the Vancouver and Hamilton sites. The response will be elicited by applying a square wave electrical stimulation of 0.2 ms in duration to the median and tibial nerves and recorded bilaterally and simultaneously from both hands and feet to assess the extent of disruption to spinal autonomic pathways.⁵⁷ Ten electrical stimuli, at an intensity sufficient to evoke a motor twitch (5–100 mA), will be applied in a random order, with variable and long-time delays to minimise habituation. Amplitude and latency of the SSR will also be measured. Data will be recorded using the analog-to-digital converter Dantec Keypoint® 4 system (Natus Medical Incorporated, San Carlos, CA, USA).

International autonomic standards evaluation

Until recently, individuals with SCI were only examined with the use of motor and sensory neurological standards in order to establish the level and severity of neurological impairment using the American Spinal Injury Association Impairment Scale (AIS).⁵⁸ During the last decade, international autonomic standards for the evaluation of SCI individuals were developed and implemented.⁵⁹ This evaluation collects descriptive categorical data on cardiovascular (AD and OH) and other autonomic dysfunctions including bladder, bowel and sexual functioning.

Blood haematological profile and cardiovascular disease risk biomarkers

Certified clinical laboratories at each site will analyse all blood samples. Following a 12-hour overnight fast, including no food or drink (water is permitted), alcohol or caffeine,

a trained technician will draw a venous blood sample. Complete blood cell count and biomarkers of cardiovascular disease risk will be assessed at baseline and follow-up using various analytical techniques outlined in table 4.

Body composition

Visceral adipose tissue (VAT) is closely associated with cardiometabolic disease; VAT is vascularised, more metabolically active and negatively impacts an individual's metabolic profile leading to glucose intolerance, insulin resistance and hyperlipidaemia.⁶⁰ Dual-energy X-ray absorptiometry (DXA) has been shown as a valid and reliable measure of abdominal adiposity when compared with CT and MRI.⁶¹ Furthermore, whole body DXA scans have been shown to have high levels of precision when performed on individuals with SCI.⁶²

Whole body scans will be acquired using the Hologic 4500 A or W densitometer (Waltham, Massachusetts, USA) and analysed centrally using commercially available Hologic software (V.13.4.1:5 Auto Whole Body). Routine densitometer and quality control checks will be completed daily and weekly as indicated by the manufacturer. Outcomes will be reported according to International Society for Clinical Densitometry guidelines⁶³ and include whole body fat (kg), lean soft tissue mass (kg), percentage body fat, fat mass index (kg/m²), trunk/limb fat mass ratio, android/gynoid ratio, trunk fat mass (kg), percentage trunk fat, VAT (cm²), lean soft tissue mass index (kg/m²) and appendicular lean mass index (kg/m²). Scans will be excluded from full analysis if a movement artefact is evident in any limb; only VAT outcomes will be included. If a limb is outside of the scan limit boarder, values from the contralateral side will be replicated. Height (length) will be measured using the electronic ruler function of the DXA plinth. Waist circumference will be measured in the supine position following a normal expiration to the nearest 1 cm midway between the lowest lateral border of the ribs and the uppermost

Table 4 Blood haematological and metabolic profiles

Haematological profile	Analytical techniques
CBC (white blood cells and differentials, erythrocytes, packed cell volume, haematocrit, platelets, haemoglobin and red cell indices).	Automated haematology system (Sysmex XE-2100TM, Sysmex, Mississauga, Ontario, L4W 4Y4, Canada)
CVD risk biomarkers	Analytical techniques
Lipid profile (triglycerides, TC, LDL-C, HDL-C, TC/HDL-C) and blood glucose.	Measured in plasma using an automated analyser (Cobas 8000, C701, Roche Diagnostics, Rotkreuz, Switzerland), in accordance with manufacturer's instructions via commercially available immunoassays (Roche Diagnostics, Rotkreuz, Switzerland).
Glycated haemoglobin (HbA1c).	Measured in whole blood using an automated analyser (Roche Cobas c513, Roche Diagnostics, Rotkreuz, Switzerland), in accordance with manufacturer's instructions via a commercially available immunoassay (Tina-quant HbA1c Gen. 3).

CBC, complete blood count; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

lateral iliac crest. Waist circumference is considered the most practical surrogate for VAT in individuals with SCI and is tightly associated with cardiometabolic disease biomarkers.²⁴

Cardiorespiratory fitness

Aerobic and anaerobic parameters will be assessed using a graded exercise test on an electrically braked arm-crank ergometer (Lode BV, Groningen, The Netherlands; Vancouver site, Monark 881E, Monark Exercise AB, Vansbro, Sweden; Toronto and Hamilton sites). HR will be monitored continuously using a chest strap HR monitor (T31; Polar Electro, Woodbury, New York, USA), while expired gas will be measured using a metabolic cart (Parvomedics Truemax 2400, Sandy, Utah, USA; Vancouver site: Vmax Encore, SensorMedics, California, USA; Toronto site: Moxus Metabolic System, AEI Technologies, Illinois, USA; Hamilton site). The test will begin with 2 min of resting measures including HR, cardiorespiratory variables and BP (Dinamap Carescape V100; GE Healthcare, Buckinghamshire, UK). Following this, participants will be instructed to cycle at 50 rpm for 2 min with a resistance of 0 watts as a warm-up. The test itself will last approximately 6–15 min depending on the participants' fitness level.⁶⁴ Workload will be increased every minute by 10 watts until volitional fatigue or the cadence drops below 30 rpm. A 2 min cool-down period will be provided at the end of the test. RPE will be assessed at the end of every minute using the 6–20 Borg scale, with the aim for each participant to achieve a value indicative of maximal effort (≥ 17). Peak oxygen uptake ($\text{VO}_{2\text{peak}}$) will be taken as the highest 20 s average value collected from breath-by-breath gas exchange measurements during the test. Changes in submaximal exercise capacity parameters (ie, oxygen uptake at ventilatory threshold) will also be identified using different methods.⁶⁵

Quality of life and physical activity outcomes

Several questionnaires (discussed below) will be administered over the telephone pre (0 months), during (3 months) and post-exercise (6 months) intervention and at follow-up (12 months, unless otherwise stated). All participants will be contacted by KMG.

Quality of life

Pain and general health will be assessed using subscales from the medical outcomes survey short form-36.⁶⁶ Musculoskeletal pain will also be assessed using an 11-point visual analogue scale ranging from 0 (no pain) to 10 (unbearable pain). The positive and negative affect scale (PANAS)⁶⁷ will also be completed. Participants will be asked to rate the extent to which they experience 10 negative (distressed, upset, guilty, ashamed, hostile, irritable, nervous, jittery, scared and afraid) and 10 positive (interested, alert, attentive, excited, enthusiastic, inspired, proud, determined, strong and active) emotions on a 5-point Likert scale ranging from 'very slightly' to 'very much'. Together these are generally regarded to be valid

and reliable items for assessing the impact of changes in functional status on psychological well-being.⁶⁸ The visual analogue pain scale and the PANAS will be administered pre- $\text{VO}_{2\text{peak}}$ and post- $\text{VO}_{2\text{peak}}$ testing. Life satisfaction will be assessed using the five-item satisfaction with life scale⁶⁹ and nine-item life satisfaction questionnaire.⁷⁰ Validity for both life satisfaction measures has previously been confirmed in individuals with SCI.⁷¹ To ascertain changes in self-care, mobility, respiratory and sphincter management, the spinal cord independence measure (SCIM III), which has been shown to be more sensitive to changes in function than the functional independence measure,⁷² will also be administered.

Habitual physical activity level and exercise perceptions

Self-efficacy to engage in moderate and heavy aerobic exercise will be measured, asking participants to rate how confident (1=not at all confident, 7=completely confident) they are that they can perform: (A) moderate intensity and (B) heavy-intensity activity, without stopping, for 10 min, 20 min, 30 min, 40 min, 45 min and 60 min. Items from the impact on participation and autonomy questionnaire will also be completed to determine changes in participants' indoor and outdoor autonomy and social relations (in the context of their disability). Lastly, the leisure-time physical activity questionnaire for people with SCI will be administered to determine changes in the performance of mild, moderate and heavy-intensity leisure-time physical activity. This brief questionnaire was designed specifically for individuals with SCI, with preliminary evidence showing acceptable criterion validity and reliability.⁷³

Data management

All collected data (electronic or hardcopy documents) will be coded with unique identification numbers and stored centrally on the Empower database, a password-protected computer or in a locked filing cabinet in a secure laboratory space, only accessible to the study investigators. Data transfer between each study site will be encrypted to ensure participant identity is protected from unauthorised parties. All data will be stored for 25 years after publication, after which it will be destroyed.

Statistical analysis

Linear mixed effects models, which provide a flexible framework for the analysis of longitudinal data, with the capability of estimating variance heterogeneity and within-participant residual correlations (ie, correlations among repeated within-subject measurements) will be used. The primary fixed effects for the model will be time, parameterised as either a 2-level or 3-level factor (baseline, 3 months of training and 6 months of training) (depending on the specific outcome measure); exercise group, parameterised as a two-level factor (ACET and BWSTT); and a time \times exercise group interaction. Study site will be included as a fixed-effect control factor, and the mixed effects model will be suitably flexible to permit the

inclusion of additional controlling covariates, such as sex or time since injury. The model intercept term will also be included as random effects per participant in the model. From the mixed effects model, we will generate point and interval estimates of cFPWV at each of the study evaluation time points for both intervention groups. The evaluation of the objectives will be via appropriate linear contrasts applied to the linear mixed effects model to contrast 3-month and 6-month changes in cFPWV and compare postintervention cFPWV between exercise groups. The linear contrasts for the evaluation of the objective are comparable with two-sample t-tests, and the mixed effects model, and associated contrasts, require random effects and residual normality. Should these assumptions fail, we will apply the non-parametric Wilcoxon rank sum test (stratified by study site) to compare 3-month and 6-month changes in cFPWV between exercise groups. All comparisons will be conducted at the 0.05 significance level. The trial statistician will be blinded to participant's group allocation. An intention-to-treat analysis will be performed taking into consideration participants that were withdrawn from the trial.

Power calculation and sample size

Assuming a sample size of 30 participants per exercise intervention group, a significance level of 0.05 and that the SD of cFPWV will be 10% of the baseline value (SD=1.3), these contrasts will have 80% power to detect exercise group differences of ≥ 1.0 m/s. Our target effect size of 1 m/s is in line with reported effects of exercise interventions in other high-risk populations, such as sedentary, postmenopausal women and individuals with hypertension; in these studies, 1–3 months of endurance exercise training was associated with reductions in cFPWV of 0.8 m/s⁷⁴ and 1 m/s.⁷⁵ Additionally, 1 m/s is a clinically meaningful improvement, as each 1 m/s increase in cFPWV, translates into a 15% increased risk of CV mortality.¹⁶

Safety

A Data and Safety Monitoring Committee will be composed of four individuals external and independent to the study to review adverse event (AE) reports, which will intervene and insist the study is terminated prematurely should the AE data be of sufficient concern. Any AEs reported during training will be documented with information pertaining to their severity and anatomical location. Any serious AEs will be immediately reported to the Data and Safety Monitoring Committee, as well as to the appropriate ethics boards at each site by the study coordinator.

Ethics and dissemination

Any protocol modifications will be clearly communicated to the sponsor and ethics committee. This trial will be conducted in full compliance with Good Clinical Practice, with all researchers involved having completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Course on Research Ethics.

The results of the CHOICES trial will be presented at national and international conferences and will be published in peer-reviewed journals. Any subsequent outcome manuscripts will be reported in conjunction with the Consolidated Standards of Reporting Trials.⁷⁶ Additionally, a summary of the study's findings will be posted on the ICORD website and published in the magazines of service organisations for people with SCI in the provinces where participants were recruited (ie, the SCI BC and SCI ON magazine publications). Extensive, individualised feedback will be provided to each study participant once they have completed the trial.

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Contributors AVK conceived the study and is the most responsible investigator who will oversee data collection at all sites. MJM and BCC are coprincipal investigators responsible for managing data collection at the Hamilton and Toronto study sites, respectively. The study was conceived with input from LR, JJE, KAMG, MJM, AH, DD, MCV, PO and BCC. KDC, MH, TEN, AAA and PO are responsible for data collection. All authors will be involved in data analysis and preparation of various outcome measures manuscripts. TEN and AAA wrote this protocol manuscript, the final version of which all authors have reviewed and approved.

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REFERENCES

- Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil* 2007;86:142–52.
- Lai YJ, Lin CL, Chang YJ, et al. Spinal cord injury increases the risk of type 2 diabetes: a population-based cohort study. *Spine J* 2014;14:1957–64.
- Groah SL, Weitzenkamp D, Sett P, et al. The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. *Spinal Cord* 2001;39:310–7.
- Groah SL, Nash MS, Ward EA, et al. Cardiometabolic risk in community-dwelling persons with chronic spinal cord injury. *J Cardiopulm Rehabil Prev* 2011;31:73–80.
- Nightingale TE, Williams S, Thompson D, et al. Energy balance components in persons with paraplegia: daily variation and appropriate measurement duration. *Int J Behav Nutr Phys Act* 2017;14:132.
- Krassioukov AV, Bunge RP, Puckett WR, et al. The changes in human spinal sympathetic preganglionic neurons after spinal cord injury. *Spinal Cord* 1999;37:6–13.
- Furlan JC, Fehlings MG, Shannon P, et al. Descending vasomotor pathways in humans: correlation between axonal preservation and cardiovascular dysfunction after spinal cord injury. *J Neurotrauma* 2003;20:1351–63.
- Claydon VE, Hol AT, Eng JJ, et al. Cardiovascular responses and postexercise hypotension after arm cycling exercise in subjects with spinal cord injury. *Arch Phys Med Rehabil* 2006;87:1106–14.
- Krum H, Louis WJ, Brown DJ, et al. Diurnal blood pressure variation in quadriplegic chronic spinal cord injury patients. *Clin Sci* 1991;80:271–6.
- Munakata M, Kameyama J, Kanazawa M, et al. Circadian blood pressure rhythm in patients with higher and lower spinal cord injury: simultaneous evaluation of autonomic nervous activity and physical activity. *J Hypertens* 1997;15(12 Pt 2):1745–9.
- Curt A, Nitsche B, Rodic B, et al. Assessment of autonomic dysreflexia in patients with spinal cord injury. *J Neurol Neurosurg Psychiatry* 1997;62:473–7.
- Stiens SA, Johnson MC, Lyman PJ. Cardiac rehabilitation in patients with spinal cord injuries. *Phys Med Rehabil Clin N Am* 1995;6:263–96.
- de Groot PC, Bleeker MW, van Kuppevelt DH, et al. Rapid and extensive arterial adaptations after spinal cord injury. *Arch Phys Med Rehabil* 2006;87:688–96.
- Miyatani M, Masani K, Oh PI, et al. Pulse wave velocity for assessment of arterial stiffness among people with spinal cord injury: a pilot study. *J Spinal Cord Med* 2009;32:72–8.
- Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–41.
- Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318–27.
- Hansen TW, Staessen JA, Torp-Pedersen C, et al. Ambulatory arterial stiffness index predicts stroke in a general population. *J Hypertens* 2006;24:2247–53.
- Mattace-Raso FU, van den Meiracker AH, Bos WJ, et al. Arterial stiffness, cardiorespiratory baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. *J Hypertens* 2007;25:1421–6.
- Oliver JJ, Webb DJ. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thromb Vasc Biol* 2003;23:554–66.
- Kesaniemi YK, Danforth E, Jensen MD, et al. Dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc* 2001;33:S351–8.
- Wannamethee SG, Shaper AG. Physical activity in the prevention of cardiovascular disease: an epidemiological perspective. *Sports Med* 2001;31:101–14.
- Chakravarthy MV, Joyner MJ, Booth FW. An obligation for primary care physicians to prescribe physical activity to sedentary patients to reduce the risk of chronic health conditions. *Mayo Clin Proc* 2002;77:165–73.
- Totosy de Zepetnek JO, Pelletier CA, Hicks AL, et al. Following the physical activity guidelines for adults with spinal cord injury for 16 weeks does not improve vascular health: a randomized controlled trial. *Arch Phys Med Rehabil* 2015;96:1566–75.
- Nightingale TE, Walhin JP, Thompson D, et al. Biomarkers of cardiometabolic health are associated with body composition characteristics but not physical activity in persons with spinal cord injury. *J Spinal Cord Med* 2017:1–10.
- Rosety-Rodriguez M, Camacho A, Rosety I, et al. Low-grade systemic inflammation and leptin levels were improved by arm cranking exercise in adults with chronic spinal cord injury. *Arch Phys Med Rehabil* 2014;95:297–302.
- Kim DI, Lee H, Lee BS, et al. Effects of a 6-week indoor hand-bike exercise program on health and fitness levels in people with spinal cord injury: a randomized controlled trial study. *Arch Phys Med Rehabil* 2015;96:2033–40.
- Nightingale TE, Walhin JP, Thompson D, et al. Impact of exercise on cardiometabolic component risks in spinal cord-injured humans. *Med Sci Sports Exerc* 2017;49:2469–77.
- Thijssen DH, Steendijk S, Hopman MT. Blood redistribution during exercise in subjects with spinal cord injury and controls. *Med Sci Sports Exerc* 2009;41:1249–54.
- Dietz V, Harkema SJ. Locomotor activity in spinal cord-injured persons. *J Appl Physiol* 2004;96:1954–60.
- Dobkin B, Apple D, Barbeau H, et al. Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology* 2006;66:484–93.
- Wessels M, Lucas C, Eriks I, et al. Body weight-supported gait training for restoration of walking in people with an incomplete spinal cord injury: a systematic review. *J Rehabil Med* 2010;42:513–9.
- Phillips SM, Stewart BG, Mahoney DJ, et al. Body-weight-support treadmill training improves blood glucose regulation in persons with incomplete spinal cord injury. *J Appl Physiol* 2004;97:716–24.
- Ditor DS, Kamath MV, MacDonald MJ, et al. Effects of body weight-supported treadmill training on heart rate variability and blood pressure variability in individuals with spinal cord injury. *J Appl Physiol* 2005;98:1519–25.
- Giangregorio LM, Hicks AL, Webber CE, et al. Body weight supported treadmill training in acute spinal cord injury: impact on muscle and bone. *Spinal Cord* 2005;43:649–57.
- West CR, Crawford MA, Poormasjedi-Meibod MS, et al. Passive hind-limb cycling improves cardiac function and reduces cardiovascular disease risk in experimental spinal cord injury. *J Physiol* 2014;592:1771–83.
- West CR, Crawford MA, Laher I, et al. Passive hind-limb cycling reduces the severity of autonomic dysreflexia after experimental spinal cord injury. *Neurorehabil Neural Repair* 2016;30:317–27.
- Kressler J, Nash MS, Burns PA, et al. Metabolic responses to 4 different body weight-supported locomotor training approaches in persons with incomplete spinal cord injury. *Arch Phys Med Rehabil* 2013;94:1436–42.
- Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31:2338–50.
- Miyatani M, Masani K, Moore C, et al. Test-retest reliability of pulse wave velocity in individuals with chronic spinal cord injury. *J Spinal Cord Med* 2012;35:400–5.
- Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004;21:1371–83.
- Scherr J, Wolfarth B, Christle JW, et al. Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* 2013;113:147–55.

42. Martin Ginis KA, van der Scheer JW, Latimer-Cheung AE, et al. Evidence-based scientific exercise guidelines for adults with spinal cord injury: an update and a new guideline. *Spinal Cord* 2018;56:308–21.
43. Ditor DS, Macdonald MJ, Kamath MV, et al. The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI. *Spinal Cord* 2005;43:664–73.
44. Tawashy AE, Eng JJ, Krassioukov AV, et al. Aerobic exercise during early rehabilitation for cervical spinal cord injury. *Phys Ther* 2010;90:427–37.
45. Hicks AL, Adams MM, Martin Ginis K, et al. Long-term body-weight-supported treadmill training and subsequent follow-up in persons with chronic SCI: effects on functional walking ability and measures of subjective well-being. *Spinal Cord* 2005;43:291–8.
46. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
47. Currie KD, Hubli M, Krassioukov AV. Applanation tonometry: a reliable technique to assess aortic pulse wave velocity in spinal cord injury. *Spinal Cord* 2014;52:272–5.
48. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr* 2011;24:277–313.
49. Quiñones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of doppler echocardiography: a report from the doppler quantification task force of the nomenclature and standards committee of the american society of echocardiography. *J Am Soc Echocardiogr* 2002;15:167–84.
50. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.
51. Currie KD, West CR, Krassioukov AV. Differences in left ventricular global function and mechanics in paralympic athletes with cervical and thoracic spinal cord injuries. *Front Physiol* 2016;7:110.
52. Currie KD, West CR, Stöhr EJ, et al. Left ventricular mechanics in untrained and trained males with tetraplegia. *J Neurotrauma* 2017;34:591–8.
53. Currie KD, Wong SC, Warburton DE, et al. Reliability of the sit-up test in individuals with spinal cord injury. *J Spinal Cord Med* 2015;38:563–6.
54. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996;46:1470.
55. Hubli M, Krassioukov AV. Ambulatory blood pressure monitoring in spinal cord injury: clinical practicability. *J Neurotrauma* 2014;31:789–97.
56. Hubli M, Krassioukov AV. How reliable are sympathetic skin responses in subjects with spinal cord injury? *Clin Auton Res* 2015;25:117–24.
57. Cariga P, Catley M, Mathias CJ, et al. Organisation of the sympathetic skin response in spinal cord injury. *J Neurol Neurosurg Psychiatry* 2002;72:356–60.
58. Marino RJ, Barros T, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury. *J Spinal Cord Med* 2003;26:S50–S56.
59. Alexander MS, Biering-Sorensen F, Bodner D, et al. International standards to document remaining autonomic function after spinal cord injury. *Spinal Cord* 2009;47:36–43.
60. Fox CS, Heard-Costa N, Cupples LA, et al. Genome-wide association to body mass index and waist circumference: the Framingham Heart Study 100K project. *BMC Med Genet* 2007;8 Suppl 1(Suppl 1):S18.
61. Glickman SG, Marn CS, Supiano MA, et al. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *J Appl Physiol* 2004;97:509–14.
62. Gorgey AS, Ciriigliaro CM, Bauman WA, et al. Estimates of the precision of regional and whole body composition by dual-energy x-ray absorptiometry in persons with chronic spinal cord injury. *Spinal Cord* 2018;56:987–95.
63. Petak S, Barbu CG, Yu EW, Ew Y, et al. The Official Positions of the International Society for Clinical Densitometry: body composition analysis reporting. *J Clin Densitom* 2013;16:508–19.
64. Eerden S, Dekker R, Hettinga FJ. Maximal and submaximal aerobic tests for wheelchair-dependent persons with spinal cord injury: a systematic review to summarize and identify useful applications for clinical rehabilitation. *Disabil Rehabil* 2018;40:497–521.
65. Gaskill SE, Ruby BC, Walker AJ, et al. Validity and reliability of combining three methods to determine ventilatory threshold. *Med Sci Sports Exerc* 2001;33:1841–8.
66. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
67. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–70.
68. Crawford JR, Henry JD. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br J Clin Psychol* 2004;43(Pt 3):245–65.
69. Diener E, Emmons RA, Larsen RJ, et al. The Satisfaction With Life Scale. *J Pers Assess* 1985;49:71–5.
70. Fugl-Meyer AR, Brånholm I-B, Fugl-Meyer KS. Happiness and domain-specific life satisfaction in adult northern Swedes. *Clin Rehabil* 1991;5:25–33.
71. Post MW, van Leeuwen CM, van Koppenhagen CF, et al. Validity of the Life Satisfaction questions, the Life Satisfaction Questionnaire, and the Satisfaction With Life Scale in persons with spinal cord injury. *Arch Phys Med Rehabil* 2012;93:1832–7.
72. Catz A, Itzkovich M, Agranov E, et al. SCIM--spinal cord independence measure: a new disability scale for patients with spinal cord lesions. *Spinal Cord* 1997;35:850–6.
73. Martin Ginis KA, Phang SH, Latimer AE, et al. Reliability and validity tests of the leisure time physical activity questionnaire for people with spinal cord injury. *Arch Phys Med Rehabil* 2012;93:677–82.
74. Figueroa A, Park SY, Seo DY, et al. Combined resistance and endurance exercise training improves arterial stiffness, blood pressure, and muscle strength in postmenopausal women. *Menopause* 2011;18:980–4.
75. Collier SR, Kanaley JA, Carhart R, et al. Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre- and stage-1 hypertensives. *J Hum Hypertens* 2008;22:678–86.
76. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *J Pharmacol Pharmacother* 2010;1:100–7.